*Chemistry of Natural Compounds, Vol. 30, No. 5, 1994*

# SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS
## VII. SYNTHESIS OF 1,3-BENZODIOXANE ANALOGS OF DEHYDROSILYBIN

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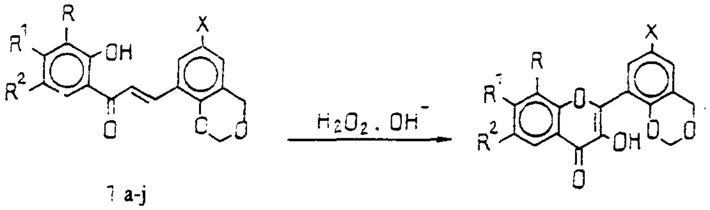
UDC 547.814.5

*Structural analogs of dehydrosilbyn have been obtained from 1,3-benzodioxane derivatives of chalcones. Their structures have been confirmed by their PMR spectra.*

We have previously [1] reported the synthesis of simpler analogs of silybin and dehydrosilybin. With the aim of elucidating the influence on the properties of silybin and dehydrosilybin of various modifications to them, we have investigated the synthesis of structurally isomeric analogs of these substances.

As the initial reactants we took the chalcones (1), described in [2, 3]. The oxidation of chalcones (1a-j*) with hydrogen peroxide in an alkaline medium under the conditions of the Algar—Flynn—Oyamada (AFO) reaction [4] led exclusively to the 3-hydroxychromones (2a-j*). In some cases, salicylic acid derivatives were isolated as by-products.



1 a-j

2 a-j

a: $R^2$=Cl, X=Cl; b: $R^1$=Me, X=Br; c: $R^2$=Cl, X=Br; d: $R^2$=EtO, X=Br; e: $R^1$=Me, X=COOH; g: $R^2$=Me, X=COOH; h: $R^1$=$R^2$=Me, X=COOH; i: $R^2$=Cl, X=COOH; j R=$R^2$=Cl, X=COOH.

The 3-hydroxychromones (2) obtained consisted of colorless or light yellow crystalline substances with high melting points sparingly soluble in organic solvents. The structures of the compounds obtained were confirmed by the results of analyses and by PMR spectra (Tables 1 and 2).

In the PMR spectra of the 3-hydroxychromones (2) measured in DMSO-$d_6$ the OH-3 group appeared in the 9.1-9.6 ppm region. The H-5 aromatic protons of the chromone rings gave peaks in the 7.6-8.1 ppm interval, while the protons of the methylenedioxy groups gave singlets at 5.3-5.4 ppm ($CH_2$-2) and 4.9-5.0 ppm ($CH_2$-4). The protons of the carboxy groups appeared in the form of broadened singlets in a weaker field (12.2-12.8 ppm).

Thus, the reaction of 1,3-benzodioxane chalcone analogs with hydrogen peroxide under the AFO conditions has enabled us to synthesize the corresponding dehydrosilybin analogs with good yields. A study of the biological properties of the new dehydrosilybin analogs has shown that some representatives of these compounds possess hepatoprotective and cholagogic activities.

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*No compounds (1f) and (2f) are mentioned in this paper — Translator.

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0009-3130/94/3005-0573$12.50

TABLE 1. Characteristics of Compounds (2)

| Compound | Yield, % | mp, °C | Empirical formula | Solvent for crystallization |
|---|---|---|---|---|
| 2a | 53 | 241—243 | $C_{17}H_{10}Cl_2O_5$ | EtOAc |
| 2b | 63.4 | 240—242 | $C_{18}H_{13}BrO_5$ | $CH_3COOH$ |
| 2c | 71.9 | 256—258 | $C_{17}H_{10}BrClO_5$ | $CH_3COOH$ |
| 2d | 48.7 | 247—248 | $C_{19}H_{15}BrO_6$ | EtOAc |
| 2e | 34.3 | >300 | $C_{19}H_{14}O_7$ | DMFA |
| 2g | 37.1 | >310 | $C_{19}H_{14}O_7$ | $CH_3COOH$ |
| 2h | 30.9 | >310 | $C_{20}H_{16}O_7$ | $CH_3COOH$/DMFA |
| 2i | 40.4 | 302—304 | $C_{18}H_{11}ClO_7$ | $CH_3COOH$/DMFA |
| 2j | 45.6 | >300 | $C_{18}H_{10}Cl_2O_7$ | DMFA/$H_2O$ |

TABLE 2. PMR Spectra (δ, ppm, J, Hz) of the 1,3-Benzodioxane Analogs of Dehydrosilybin (2) in DMSO-$d_6$

| Compound | Chromone protons | | | | | Benzodioxane protons | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OH-3, s | H-5 | $R^2$-6 | $R^1$-7 | R-8 | H-5, d, (2.44) | H-7, d, (2.44) | COOH-6, s | $CH_2$-2, s | $CH_2$-4, s |
| 2a | 9.45 | 8.07 d, (2.0) | – | 7.83 d.d, (8.0; 2.0) | 7.72 d, (8.0) | 7.39 | 7.51 | | 5.29 | 4.96 |
| 2b | 9.12 | 8.00 d, (8.3) | 7.28 d.d, (8.3; 1.46) | 2.45 s | 7.43 d, (1.46) | 7.48 | 7.60 | | 5.29 | 4.96 |
| 2c | 9.43 | 8.08 d, (2.0) | – | 7.84 d.d, (8.5; 2.0) | 7.69 d, (8.5) | 7.50 | 7.63 | | 5.28 | 4.95 |
| 2d | 9.14 | 7.47 d, (1.46) | 4.15 q; 1.38 t | 7.36 d.d, (8.3; 1.46) | 7.59 d, (8.3) | 7.48 | 7.60 | | 5.29 | 4.95 |
| 2e | 9.16 | 8.02 d, (8.3) | 7.29 d.d, (8.3; 1.46) | 2.45 s | 7.45 d, (1.46) | 7.85 | 8.00 | 12.2 | 5.37 | 5.04 |
| 2g | 9.18 | 7.93 d, (1.46) | 2.45 s | 7.56 m | 7.56 m | 7.86 | 8.00 | 12.7 | 5.38 | 5.04 |
| 2h | 9.06 | 7.86 s | 2.36 s | 2.36 s | 7.43 s | 7.83 | 7.97 | 12.8 | 5.37 | 5.03 |
| 2i | 9.42 | 7.6—8.1 m | – | 7.6—8.1 m | 7.6—8.1 m | 7.73 | 8.04 | 12.82 | 5.37 | 5.02 |
| 2j | 9.65 | 8.13 d, (2.0) | – | 8.05 d, (2.0) | – | 7.87 | 8.05 | 12.7 | 5.38 | 5.04 |

## EXPERIMENTAL

The conditions for recording the spectra are described in [3].

**2-(1,3-Benzodioxan-8-yl)-3-hydroxychromones (2a-j).** A suspension of 3 mmole of one of the chalcones (1a-j) in 20 ml of methanol was treated with 5 ml of a 4 N solution of caustic soda (10 ml in the case of 6-carboxy-1,3-benzodioxane) and 1.2 ml of a 30% solution of hydrogen peroxide. The reaction mixture was kept at room temperature for 48 h and was then diluted with water and neutralized with dilute hydrochloric acid to pH 7. The precipitate that deposited was filtered off and was crystallized from a suitable solvent.

## REFERENCES

1. V. P. Khilya and A. Aitmambetov, Khim. Prir. Soedin., 351 (1994).
2. V. P. Khilya, Kh. Al' Budi [H. Al Budy], A. Aitmambetov, L. G. Grishko, A. V. Zakharik, and D. Litkei, Khim. Geterotsikl. Soedin., No. 7, 879 (1992).
3. A. Aitmambetov, D. M. Zakharik, and V. P. Khilya, Khim. Prir. Soedin., No. 4, 484 (1994).
4. M. G. Marathey, J. Org. Chem., **20**, No. 5, 563 (1955).